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By: Diane Kizer Printed: Diane Kizer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: LaDine, et al.

Serial No.: 09/835,273

Examiner: Michael L. Borin

Filed: 04/13/2001

Art Unit: 1631

Title: Proteomic Analysis by Parallel Mass Spectrometry

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF AMENDED BRIEF

Responsive to the Notification of Non-Compliant Appeal Brief mailed on 10/25/2006 relating to the above-identified application, submitted herewith is an Amended Appeal Brief that corrects the noted deficiencies.

It is believed that no further fees are required for this submission; however, if this belief is inaccurate, the Commissioner is hereby authorized to charge any required fees to Deposit Account No. 50-3267.

Dated: November 10, 2006

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James R. LaDine et al. Art Unit : 1631
Serial No. : 09/835,273 Examiner : Michael L. Borin
Filed : April 13, 2001
Title : PROTEOMIC ANALYSIS BY PARALLEL MASS SPECTROMETRY

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDED BRIEF ON APPEAL

(1) Real Party in Interest

The real party in interest is Thermo Finnigan LLC, by virtue of an assignment from the inventors recorded in the U.S. Patent Office on January 7, 2002, Reel 012434, Frame 0382.

(2) Related Appeals and Interferences

There are no related appeals or interferences known to the appellant.

(3) Status of Claims

Claims 1-2, 5-18, 22-45 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Zenhausern (U.S. Pub. No. 2002/0094531; hereinafter "Zenhausern") taken alone, and over Chang et al. (U.S. Pat. No. 4,507,555; hereinafter "Chang") and Demirev et al. (Anal. Chem. (1997), 69(15), 2893-2900; hereinafter "Demirev") and Chalmers et al. (hereinafter "Chalmers") in view of Zenhausern, Henry et al. (Anal. Chem. (1999), 71(7), 264A-268A; hereinafter "Henry"), Cotter et al. (J. Mass Spectrometry (1999), 34, 1368-1372; hereinafter "Cotter"), and Orient et al. (Rev. Sci. Instr. (1997), 68(3), 1393-1397; hereinafter "Orient"). Claims 3-4 and 19-21 have been cancelled. No claims have been allowed.

(4) Status of Amendments

There are no amendments filed subsequent to final rejection. All amendments were made prior to the final rejection.

(5) Summary of the Claimed Subject Matter

Independent claims 1, 22 and 29 in the application are presented for appeal. Claim 1 is directed to a method for analysis of proteins in a biological system. (e.g. 3:1-11[1]) The method includes providing a biological system, which is sampled at multiple time intervals to provide multiple samples, each sample containing multiple proteins. (e.g. 6:19-27; figure 1) The multiple samples are submitted to a separation technique to provide multiple protein samples suitable for analysis by mass spectrometry. (e.g. 7:3-5) The multiple samples are analyzed to determine changes in abundance of proteins as a function of time. (e.g. 7:21-26) The analysis includes allocating the multiple protein samples for the multiple samples among mass spectrometry systems in a parallel array of mass spectrometry systems, such that each mass spectrometer system analyzes a different one of the multiple protein samples. (e.g. 7:15-16, 7:26-8:3; figure 1) Each mass spectrometry system is adapted for protein analysis and provides mass spectral data indicating identity and abundance of one or more proteins. (e.g. 7:23-26; figures 3, 5) The analysis also includes directing the mass spectral data from each of the mass spectrometry systems in the array to a common computing device, and collating it as a function of time of sampling of the biological system. (e.g. 7:23-25; 8:3-12)

Claim 22 is directed to a method for analysis of proteins in a biological system including: providing a biological system containing proteins (e.g. 6:20-21); exposing the biological system to a stimulus (e.g. 6:23-24; 14:12-24); after exposing the biological system to the stimulus, sampling the biological system at multiple time intervals to obtain multiple samples, each sample containing multiple proteins (e.g. 6:24-27); treating the multiple samples by a parallel separation technique to provide multiple protein samples suitable for analysis by mass spectrometry (e.g. 7:3-5); providing a parallel array of mass spectrometer systems capable of simultaneous analysis of as many protein samples as there are spectrometer systems in said array (e.g. 7:15-16, 7:26-8:3; figure 1); allocating the multiple protein samples among the mass spectrometry systems in the parallel array of mass spectrometry systems such that each mass spectrometry system analyzes a different one of the multiple protein samples to obtain mass spectral data indicating identity and abundance of proteins in said multiple protein samples (e.g. 7:15-16, 7:23-8:3;

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[1] The notation X:y-z is used herein to refer to page X, lines y through z, of the specification.

figures 1, 3, 5); communicating the mass spectral data to a common computing device (e.g. 8:3-9); and collating said mass spectral data as a function of time (e.g. 7:23-28; 8:10-12).

Claim 29 is directed to a system for mass spectrometric analysis of proteins in a biological system. (e.g. 3:24-30) The system includes a parallel sample separation apparatus adapted to receive multiple samples of a biological system taken at multiple time intervals and separate the multiple samples in parallel to obtain multiple protein samples for analysis by mass spectrometry. (e.g. 6:19-27; 14:1-9; figure 4) The system also includes a parallel array of mass spectrometry systems adapted to receive the multiple protein samples from the separation apparatus and analyze the multiple protein samples in parallel to generate mass spectral data indicating identity and abundance of proteins, each mass spectrometry system analyzing a different one of the multiple protein samples. (e.g. 7:15-16, 7:26-8:3, figure 1) A computing device communicates with the parallel array of mass spectrometry systems and the parallel separation apparatus, and is adapted to analyze the mass spectral data from the parallel array of mass spectrometry systems and collate the mass spectral data as a function of time of sampling. (e.g. 7:23-25; 8:3-12)

Embodiments of the invention may include one or more of the following features, which are recited in the various dependent claims. The separation technique includes use of one or more separation apparatus and the common computing device communicates with each of the separation apparatus. The separation technique includes use of an array of parallel separation apparatus. (e.g. figure 4) The array of separation apparatus treats multiple samples in parallel. (e.g. 8:19-22) The array of separation apparatus treats multiple samples in parallel and the array of mass spectrometry systems treats multiple samples in parallel. (e.g. figure 4) The number of separation apparatus in the array of parallel separation apparatus is equal to the number of mass spectrometry systems in the array of parallel mass spectrometry systems. (e.g. 14:1-9) A first portion of the multiple protein samples are allocated among the mass spectrometry systems before a second portion of the multiple protein samples have been provided by the separation technique. (e.g. 7:26-29). Treatment of multiple samples by the array of separation apparatus is carried out in parallel with treatment of multiple samples by the array of mass spectrometry systems. (e.g. 7:26-29)

(6) Grounds of Rejection for Review

A. Are claims 1-2, 5-18, and 22-45 properly rejected under 35 U.S.C. §103(a) as unpatentable over Zenhausern?

B. Are claims 1-2, 5-18, and 22-45 properly rejected under 35 U.S.C. §103(a) as unpatentable over Chang and Demirev and Chalmers in view of Zenhausern, Henry, Cotter and Orient?

(7) Arguments

Prior to turning to the specific rejections, the applicant believes that it may be helpful to offer a general discussion of the principal novel features of the claimed invention. Each of the independent claims (1, 22 and 29) is directed to a workflow or instrument array architecture by which multiple protein samples are allocated among individual mass spectrometer systems of an interconnected array of mass spectrometer systems, such that the multiple protein samples may be concurrently analyzed. The multiple protein samples represent different fractions of a sample taken from a biological system at a particular sampling time. The results of the mass analyses performed at the individual mass spectrometers are conveyed to a common computing device, which collates the results as a function of the time of sampling. In this manner, the effect of a stimulus (e.g., a pharmaceutical agent) on the proteome (a collection of a large number of proteins) of a human or animal subject may be observed over time.

Utilization of the claimed parallel mass spectrometer system array architecture has significant advantages over the prior art. As is discussed in the specification (2:10-29) of the present application, a single time-resolved study of the effect of a stimulus on a cell proteome would take an unacceptably long time to complete if the mass spectrometric analyses are performed serially. By concurrently analyzing individual protein samples in corresponding mass spectrometer systems arranged in an interconnected array, proteomic analysis may be conducted on a practical time scale.

The examiner has wholly failed to provide any credible support in the prosecution record, either in the form of a publication or articulated general knowledge, for his contention that the claimed interconnected parallel arrays of mass spectrometer systems were known in or suggested

by the prior art. Given the absence of such support, the examiner's rejections under §103(a) are improper and should be reversed.

A. Are claims 1-2, 5-18, and 22-45 properly rejected under 35 U.S.C. §103(a) as unpatentable over Zenhausern?

Claim 1, as finally rejected, recites a method for the analysis of multiple samples containing multiple proteins taken from a biological system at multiple time intervals. The samples are submitted to a separation technique and the resulting multiple protein samples are then allocated among mass spectrometry systems in an array of mass spectrometry systems. Each mass spectrometry system analyzes a different one of the protein samples and provides mass spectral data indicating identity and abundance of one or more proteins in the sample. A common computing device then collates the mass spectral data, for the multiple protein samples from the multiple samples, as a function of the time of sampling of the biological system.

The remainder of the independent claims (22 and 29) in the application also recite analysis of multiple samples containing multiple proteins taken from a biological system at multiple time intervals; an array of mass spectrometry systems, each system analyzing a different protein sample to provide spectral data indicating identity and abundance of one or more proteins; and collating by a common computing device of mass spectral data from the array of mass spectrometry systems as a function of the time of sampling.

The Examiner has repeatedly mischaracterized the teachings of Zenhausern in his rejections. Zenhausern describes a multisensor array comprised of a plurality of sensors (also variously referred to as probes or sensing probes). Per paragraphs 0047, 0059, and 0069, one or more sensors of the array may take the form of a mass spectrometer. However, Zenhausern does not teach that its multisensor array can be used to conduct parallel analysis of different samples (i.e., where each sensor of the array senses a different sample, protein or otherwise), nor does it suggest how the array may be modified to do so. Rather (as best as can be understood by the applicant in view of the lack of clarity of the Zenhausern disclosure), each sensor of the array is configured to sense a different property, molecule, or combination of molecules within a single sample, such that the multisensor array detects more than one physical, chemical, or physicochemical change characterizing the monitored reaction. The sections of Zenhausern cited

by the Examiner in the Office Action dated May 15, 2006 (claim 1 and paragraphs 0047, 0068, and 0070) in support of his argument that Zenhausern teaches parallel processing of multiple distinct samples, as claimed in the present Application, merely describe the operation of a multi-sensor array to simultaneously acquire data from a single sample representative of different properties or molecular components of the single sample.

Even if it were possible to modify the multisensor array of Zenhausern such that it could be used to analyze multiple distinct samples in a parallel fashion, as presently claimed, the Examiner has not offered any reason, motivation or suggestion to do so. In the absence of such reason, motivation or suggestion, the rejections of independent claims 1, 22 and 29 under §103(a) are improper and should be reversed. See, e.g., *In re Fritch*, 972 F.2d 1260, 23 U.S.P.Q. 1780, 1783-84 (Fed. Cir. 1992); M.P.E.P. §2143.01(I)("The Prior Art Must Suggest the Desirability of the Claimed Invention").

Dependent claims 2, 5-18, 23-28 and 30-45 are submitted to be patentable over Zenhausern for substantially the same reasons advanced above in connection with the independent claims from which they depend. Reversal of the Examiner's rejection of these claims under §103(a) is therefore believed to be in order.

B. Are claims 1-2, 5-18, and 22-45 properly rejected under 35 U.S.C. §103(a) as unpatentable over Chang and Demirev and Chalmers in view of Zenhausern, Henry, Cotter and Orient?

Claims 1-2, 5-18, and 22-45 also stand rejected as unpatentable over Chang and Demirev and Chalmers in view of Zenhausern, Henry, Cotter and Orient. Applicant submits that this ground of rejection is also improper for the reasons set forth below.

Neither Demirev nor Chang describes or suggests the use of an array of mass spectrometry systems, each system providing mass spectral data indicating identity and abundance of one or more proteins, let alone the use of an array of mass spectrometry systems for the analysis of multiple samples that have each been separated into multiple protein samples, as required by the pending independent claims.

Demirev describes statistics that can be used to characterize the diversity in a combinatorial library of peptides in a single sample, e.g. by calculating the mean and standard

deviation of mass spectrometry signals generated for the combinatorial library of peptides. This "massively parallel" (p. 2900) approach characterizes a combinatorial or "parallel" library of peptides by the distribution of its mass spectral patterns instead of the possibly difficult-to-obtain identities of the constituents. It is not a method for analyzing the identities and abundances of proteins in multiple protein samples with a parallel array of mass spectrometers, as required by the pending independent claims.

Chang describes the use of a special mass spectrometry system to analyze a single sample. The system is referred to as a "parallel" mass spectrometer (PMS) because it has two or more sets of ion extraction means, mass resolution devices, and ion detectors that are connected in parallel rather than in tandem. This type of mass spectrometer provides for two simultaneous analyses of the components in a single sample. But there is no parallel array of mass spectrometry systems that analyzes multiple protein samples (each of which may have a plurality of components) from multiple samples, as required by the pending independent claims.

In the Office Action dated September 30, 2005, the Examiner admitted on page 5 that "the primary references [Chang and Demirev] do not teach multiple system[s] of parallel mass-spectrometers that analyze the separated protein samples- in these references multiple samples are analyzed by the same mass-spectrometer, or a duet of mass spectrometers analyzing various aspects of the same sample." The Examiner then asserted that "the idea of combining of [sic] several analytical devices is well known in the art" and proceeded to cite Zenhausern and Henry, Cotter and Orient in support of this assertion.

Applicant first notes that, while the general concept of combining several analytical devices may indeed be well-known in the art, none of the cited prior art references describe the architecture and workflow embodied in the independent claims of the present invention, whereby multiple samples are allocated among individual mass spectrometer systems of an interconnected array such that each sample is analyzed by a different mass spectrometer system. Furthermore, general knowledge that analytical devices can be combined does not in and of itself suggest the claimed architecture or workflow.

With respect to the Zenhausern reference, the applicant notes again that Zenhausern describes an arrangement of sensors (one or more of which may be mass spectrometers) that is fundamentally different in both form and function from the claimed mass spectrometer system.

More specifically, Zenhausern teaches a multi-sensor array that is configured to simultaneously acquire data from a single sample representative of different properties or molecular components of the single sample. Zenhausern does not suggest to one of ordinary skill in the art how individual mass spectrometer systems (including those mass spectrometer systems disclosed in the Chang and Demirev references) may be combined into an interconnected array capable of concurrent analysis of multiple samples, and how the results of those analyses may be collated, as recited in the claims.

The remaining references relied upon by the Examiner (Henry, Cotter and Orient) merely disclose simplified and/or miniaturized designs for individual mass spectrometers. Even assuming for the purpose of argument that the mass spectrometer designs disclosed in the Henry, Cotter and Orient papers are "better suited for combining into such mass spectrometer arrays" (per page 6 of the aforementioned Office Action), nothing in these references does in fact teach or suggest the combination of multiple mass spectrometers into an interconnected array of the type claimed in the present application.[2] The combination of the Henry, Cotter and/or Orient references with Zenhausern still does not produce the claimed subject matter, since, as argued repeatedly by the applicant, Zenhausern teaches a fundamentally different arrangement and method of operation whereby arrays of a multi-sensor array simultaneously acquire data from a single sample representative of different properties or molecular components of the single sample.

The applicant recognizes that a rationale for combining or modifying references can be implied or reasoned from the prior art or from knowledge generally available to one of ordinary skill in the art. The applicant further recognizes that it is proper to take into account the inferences that one of skill in the art would reasonably be expected to draw from a reference. But the elements of the claims are not even described in the cited references, and the Examiner has provided no line of reasoning and no basis for inferring the claimed invention from the description of mass spectrometry systems and the idea of parallel analysis represented in the cited references.

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[2] Both Henry and Orient disclose the combination of miniaturized mass analyzers into arrays. However, in each case, a single ion source is contemplated, such that the individual mass analyzers concurrently analyze ions produced from a common ion source.

In the absence of a convincing line of reasoning, the only basis for such a modification to the relied-upon references is the hindsight provided by applicant's claims – and the use of hindsight to establish a prima facie case of obviousness is simply not proper. See *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985); *In re Dembiczak,* 175 F.3d 994 (Fed. Cir. 1999) *abrogated on other grounds in In re Gartside,* 203 F.3d 1305 (Fed. Cir. 2000) (noting the "subtle but powerful attraction of a hindsight-based obviousness analysis" and requiring a "rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references); MPEP 2142, paragraph 2.

Moreover, the Board of Appeals cannot simply rely on the Examiner's knowledge or its own knowledge as skilled artisans. There must be an evidentiary record that demonstrates the presumed knowledge and establishes the obviousness of the invention. *In re Kotzab,* 217 F.3d 1365, 1371 (Fed. Cir. 2000) ("[P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed."); see also *In re Lee*, 277 F.3d 1338, 1343, 1345 (Fed. Cir. 2002) ("[When relying on] general knowledge to negate patentability, that knowledge must be articulated and placed on the record.") There is no such record here.

For the foregoing reasons, the applicant respectfully submits that no prima facie case of obviousness under 35 U.S.C. § 103 has been established with respect to the independent claims of the present application. Further, dependent claims 2, 5-18, 23-28 and 30-45 are submitted to be patentable over the prior art references of record for substantially the same reasons advanced above in connection with the independent claims from which they depend. Reversal of the Examiner's rejection of these claims under §103(a) is therefore believed to be in order.

The Director is hereby authorized to charge any other fees required by this submission, and to credit any overpayment, to Deposit Account No. 50-3267.

Respectfully submitted,

Date: 9 November 2006

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Claims Appendix

1. A method for analysis of proteins in a biological system comprising:

providing a biological system;

sampling the biological system at multiple time intervals to provide multiple samples, each sample containing multiple proteins;

submitting each of the multiple samples to a separation technique to provide multiple protein samples suitable for analysis by mass spectrometry; and

analyzing the multiple samples to determine changes in abundance of proteins as a function of time, said analyzing including

allocating the multiple protein samples for the multiple samples among mass spectrometry systems in a parallel array of mass spectrometry systems, each mass spectrometry system analyzing a different one of the multiple protein samples and providing mass spectral data indicating identity and abundance of one or more proteins,

directing mass spectral data from each of the mass spectrometry systems in said array to a common computing device, and

collating said mass spectral data from each of the mass spectrometry systems as a function of time of sampling of the biological system.

2. The method of claim 1 further comprising displaying said collated data as a function of protein identity, protein abundance, and time.

3. (Canceled)

4. (Canceled)

5. The method of claim 1 wherein said array of mass spectrometry systems includes at least 5 mass spectrometers.

6. The method of claim 1 wherein analyzing the multiple samples includes analyzing the multiple samples to determine changes in abundance of 500 proteins or more.

7. The method of claim 1 wherein analyzing the multiple samples includes analyzing the multiple samples to determine changes in abundance of about 5000 proteins or more.

8. The method of claim 1 wherein the separation technique includes use of one or more separation apparatus and said common computing device communicates with each of said separation apparatus.

9. The method of claim 1 wherein the separation technique includes use of liquid chromatography.

10. The method of claim 8 wherein the separation apparatus includes a magnetic particle separation apparatus.

11. The method of claim 38 wherein the array of separation apparatus treat multiple samples in parallel.

12. The method of claim 1 wherein the separation technique includes treating each of the multiple protein samples with a protease to produce peptides and the mass spectral data includes amino acid sequence data that can be compared to amino acid sequence data derived from a data base.

13. The method of claim 12 wherein said mass spectrometry systems are LC-TMS mass spectrometers.

14. The method of claim 1 further comprising:

exposing a first instance of the biological system to a stimulus and maintaining a second instance of the biological system free of the stimulus;

wherein sampling, submitting, and analyzing include sampling, submitting, and analyzing each of the first and the second instances; and

correlating mass spectral data includes comparing mass spectral data from the first and the second instances.

15. The method of claim 14 comprising separately analyzing samples from said first component and second component.

16. The method of claim 43 wherein the perturbation results from exposure of the biological system to heat, light, cold, motion, agitation, cellular material, or a drug.

17. The method of claim 1 wherein the time interval is about 5 to 60 seconds.

18. The method of claim 1 wherein the time interval is about one minute to one hour.

19-21. (Cancelled)

22. A method for analysis of proteins in a biological system comprising:

providing a biological system containing proteins;

exposing the biological system to a stimulus;

after exposing the biological system to the stimulus, sampling the biological system at multiple time intervals to obtain multiple samples, each sample containing multiple proteins;

treating the multiple samples by a parallel separation technique to provide multiple protein samples suitable for analysis by mass spectrometry;

providing a parallel array of mass spectrometer systems capable of simultaneous analysis of as many protein samples as there are spectrometer systems in said array;

allocating the multiple protein samples among the mass spectrometry systems in the parallel array of mass spectrometry systems such that each mass spectrometry system analyzes a different one of the multiple protein samples to obtain mass spectral data indicating identity and abundance of proteins in said multiple protein samples;

communicating the mass spectral data to a common computing device; and

correlating said mass spectral data as a function of time.

23. The method of claim 22 wherein the parallel separation technique is performed using a parallel magnetic particle separation device.

24. The method of claim 23 wherein the parallel array of mass spectrometry systems includes an array of LC-MS spectrometer systems.

25. The method of claim 24 wherein the array includes 6-20 mass spectrometers.

26. The method of claim 25 wherein the time intervals are in the range of 5 seconds to 10 minutes.

27. The method of claim 26 wherein the analysis includes analysis of about 500 proteins or more.

28. The method of claim 23 wherein the central computer communicates with the parallel magnetic particle separation device.

29. A system for mass spectrometric analysis of proteins in a biological system, the system comprising:

a parallel sample separation apparatus adapted to receive multiple samples of a biological system taken at multiple time intervals, and separate the multiple samples in parallel to obtain multiple protein samples for analysis by mass spectrometry;

a parallel array of mass spectrometry systems adapted to receive the multiple protein samples from the separation apparatus and analyze the multiple protein samples in parallel to generate mass spectral data indicating identity and abundance of proteins, each mass spectrometry system analyzing a different one of the multiple protein samples; and

a computing device communicating with the parallel array of mass spectrometry systems and the parallel separation apparatus, the computing device being adapted to analyze the mass spectral data from the parallel array of mass spectrometry systems and collate the mass spectral data as a function of time of sampling.

30. The system of claim 29, wherein the parallel separation device is a parallel magnetic particle separation device.

31. The system of claim 29, wherein the parallel separation device is a parallel chromatography separation device.

32. The system of claim 29, wherein the computing device is adapted to collate the mass spectral data as a function of time.

33. The system of claim 29, further comprising a graphical user interface that can be searched, queried, or filtered to display selected collated data.

34. The system of claim 29 wherein the parallel array of mass spectrometry systems includes at least 5 mass spectrometers.

35. The system of claim 29, wherein the parallel array of mass spectrometry systems includes at least 20 mass spectrometers.

36. The system of claim 29, wherein the parallel array of mass spectrometry systems is adapted to generate mass spectral data including peptide fragment mass spectra, and the computing device is adapted to analyze the mass spectral data in conjunction with an amino acid sequence derived from a database.

37. The system of claim 29, wherein the parallel array of mass spectrometry systems include a liquid chromatograph-tandem mass spectrometer system.

38. The method of claim 8 wherein a first portion of the multiple protein samples are allocated among the mass spectrometry systems before a second portion of the multiple protein samples have been provided by the separation technique.

39. The method of claim 8 wherein the separation technique includes use of an array of parallel separation apparatus.

40. The method of claim 39 wherein the number of separation apparatus in the array of parallel separation apparatus is equal to the number of mass spectrometry systems in the array of parallel mass spectrometry systems.

41. The method of claim 11 wherein the array of mass spectrometry systems treat multiple samples in parallel.

42. The method of claim 41 wherein treatment of multiple samples by the array of separation apparatus is carried out in parallel with treatment of multiple samples by the array of mass spectrometry systems.

43. The method of claim 1 further comprising exposing the biological system to a perturbation, wherein sampling of the biological system occurs at multiple time intervals after the exposure of the biological system to the perturbation.

44. The method of claim 1 further comprising inferring interactions over time between and among proteins in the biological system.

45. The method of claim 2 wherein protein abundance is expressed as relative abundance of proteins in each of the multiple samples.

Evidence Appendix

None

Related Proceedings Appendix

None